REMARKS

Amendments to the Specification

The specification has been amended to address the Office's comments regarding the trademark "MATRIGEL". Specifically, the specification has been amended to capitalize the trademark "MATRIGEL" where found in the specification. The specification has also been amended to delete a citation to a website on page seven. The specification has also been amended to include the proper demarcation for other trademarks found in the specification.

No new matter has been added by way of these amendments.

Amendments to the Claims

Claims 1-25 are pending in this application. With the present submission, claims 5, 7-15, and 18-25 have been withdrawn without prejudice, as directed to non-elected subject matter. Claim 2 and claim 17 have been canceled without prejudice as being redundant in view of the amendments to claim 1 and claim 16, respectively. Claims 1, 3, 4, 6, and 16 have been amended. New claims 26-28 have been added.

Specifically, claim 1 has been amended to recite: "[a] method of identifying a candidate Checkpoint kinase (CHK) pathway modulating agent, said method comprising the steps of: (a) providing an assay system comprising cultured cells that express a p21/CDC42/RAC1-activated kinase (PAK) polypeptide or nucleic acid; (b) contacting the assay system with a test agent that modulates the expression and/or activity of a PAK nucleic acid or polypeptide under conditions whereby, but for the presence of the test agent, the system provides a reference activity; and (c) detecting a test agent-biased activity of the assay system, wherein a difference between the test agent-biased activity and the reference activity identifies the test agent as a candidate CHK pathway modulating agent." Amended claim 1 finds support in the as-filed application at, *inter alia*, pages 3, 8-10, and 12-19.

Claim 3 has been amended merely to correct the dependency and correct matters of form. Claim 4 has been amended merely to correct matters of form. Claim 6 has been amended to correct matters of form and to delete non-elected subject matter from the claim. Claim 6 has been amended merely to delete reference to the non-elected inventions.

Claim 16 has been amended to recite: "[t]he method of Claim 1, comprising the additional steps of: (d) providing a second assay system capable of detecting a change in the CHK pathway comprising cultured cells that express a PAK polypeptide or nucleic acid; (e) contacting the second assay system with the test agent of (b) or an agent derived therefrom; and (f) determining a change in the CHK pathway in the second assay system, wherein a change in the CHK pathway between the presence and absence of said test agent or agent derived therefrom confirms the test agent or an agent derived therefrom as a candidate CHK modulating agent." Amended claim 16 finds support in the as-filed application at, *inter alia*, pages 3, 4, and 30-32.

New claim 26 recites "[t]he method of claim 1, wherein the agent is a small molecule modulator, a nucleic acid modulator, or an antibody." New claim 26 finds support in original claim 22 and in the as-filed application at, *inter alia*, pages 13-14, 15-18, and 18- 19.

New claim 27 recites "[t]he method of claim 26, wherein the nucleic acid modulator is an antisense oligomer." New claim 27 finds support in original claim 9 and in the as-filed application at, *inter alia*, page 18.

New claim 28 recites "[t]he method of claim 26, wherein the nucleic acid modulator is a phosphothioate morpholino oligomer (PMO)." New claim 28 finds support in original claim 10 and in the as-filed application at, *inter alia*, page 18.

The claim amendments are made solely in an effort to advance prosecution and are made without prejudice or disclaimer, without intent to acquiesce in any rejection of record, and without intent to abandon any previously claimed subject matter. Additionally, these amendments and cancellation are not and should not be construed as

admissions regarding the patentability of the claimed or canceled subject matter. Applicants reserve the right to pursue the subject matter of previously presented claims in this or in any other appropriate patent application. No new matter has been added by way of these amendments. Accordingly, Applicants respectfully request the entry of the amendments presented.

Objection to the Specification

The specification was objected to because the trademark "MATRIGEL" was not capitalized. The specification has been amended to address this objection. Applicant respectfully requests withdrawal of the objection to the specification.

35 USC § 112, First Paragraph, Rejections

Enablement

Claims 1-4, 6, 16 and 17 were rejected under 35 USC § 112, first paragraph, as allegedly failing to comply with the enablement requirement. Claims 2 and 17 have been canceled, rendering the rejection moot with respect to these claims. Applicants respectfully traverse the rejection with respect to claims 1, 3, 4, 6, and 16.

The Office Action argued that the claims are not enabled because allegedly the specification does not clearly teach the elements of the claimed methods. Specifically, the Office appears confused as to the relationship between Chk1 and PAK, and their individual associations with the CHK pathway. Specifically, the Office alleges that the specification fails to clearly set forth (1) how PAKs modulate the CHK pathway and (2) what constitutes PAK, i.e., whether a PAK is any molecule that modulates chk1 or the CHK pathway, or is a p21 activated kinase. In addition, the Office states that the role of PAK in the claimed method is not clear because the claim fails to require any active role of the PAK in the method. The Office Action further states that the specification and art of record fail to establish a link between the CHK1 pathway and PAKs (known in the art as p21 activated kinases) and also fail to define PAKs as modulators of CHK1. Therefore, the Office Action concludes that "it would require undue experimentation for

one of ordinary skill in the art to carry out the invention as claimed given the lack of clear teachings in the specification." Office Action, page 4.

In response, Applicants submit that the specification clearly teaches the elements of the claimed methods. First, the specification clearly teaches what constitutes chk1, PAK, and the CHK pathway. On page 1, the specification discusses regulation of the cell cycle, including various cell cycle phases and checkpoints, and the components associated therewith. One skilled in the at would know from the teaching in the specification and the art that the term "CHK pathway" refers to the various checkpoints that regulate the cell cycle and the components associated with those checkpoints. The specification teaches that, among other things, Chk1 is an essential component of the G2 DNA damage checkpoint and can also cause a G1 cell cycle arrest or apoptosis by stabilizing p53. Chk1 is activated by the DNA damage sensor, ATR, and the checkpoint Rad proteins in response to genotoxic stress. (specification, page 1). In contrast, the specification teaches at pages 2 and 3 that "PAKs" refer to "p21/CDC42/RAC1-activated kinase[s]" that are activated by Rho family GTPases, such as CDC42 an RAC, and may regulate cytoskeletal dynamics. Thus, PAKs are clearly defined molecules that are not the same as Chk1 and also are not considered to be "any" molecule that that modulates Chk1 or the CHK pathway as the Office suggests.

In addition, the specification clearly explains the relationship between chk1, PAK, and the CHK pathway. Specifically, the specification teaches on pages 3, 4 and 34-36 that Chk1 is a gene that modifies the CHK pathway in Drosophila and that PAK is the human ortholog of Chk1. Applicants further submit that the reason the art fails to establish a link between the CHK pathway and PAKs and also fails to define PAKs as modulators of the CHK1 pathway is because Applicants' inventive methods, based on the newly discovered link between the CHK pathway and PAK, are first described in the instant specification.

Moreover, Applicants submit that claim 1 as amended recites a method of identifying a candidate CHK pathway modulating agent using an assay system comprising cells that express a PAK polypeptide or nucleic acid and contacting the assay system with a test agent that modulates the expression and/or activity of a PAK nucleic acid or polypeptide and detecting a test agent-biased activity of the assay system, wherein

a difference between the test agent-biased activity and the reference activity identifies the test agent as a candidate CHK pathway modulating agent. Claim 16 as amended further comprises the additional steps of providing a second assay system capable of detecting a change in the CHK pathway comprising cultured cells that express a PAK polypeptide or nucleic acid, contacting the second assay system with the test agent of (b) (i.e., an agent that modulates the expression or activity of PAK), and determining a change in the CHK pathway in the second assay system, wherein a change in the CHK pathway between the presence and absence of said test agent or agent derived therefrom confirms the test agent or agent derived therefrom as a candidate CHK modulating agent.

Both of the claimed methods require contacting the assay systems comprising cells that express PAK with a test agent that modulates the expression or activity of a PAK nucleic acid or polypeptide to identify a candidate CHK pathway modulating agent. Thus, the role of PAK in the methods of claim 1 and claim 16 is clear.

Furthermore, Applicants submit that the instant claims, directed to assays for screening for a candidate CHK pathway modulating agent using an assay system comprising cultured cells that express PAK polypeptide or nucleic acid, contacting the assay system with a candidate test agent that modulates the expression and/or activity of PAK, and detecting a test agent-biased activity of the assay system, wherein a difference between the test agent-biased activity and the reference activity identifies the test agent as a candidate CHK pathway modulating agent, is fully enabled by the instant specification.

Under 35 U.S.C. §112, all that is required for satisfaction of the enablement requirement is that the specification describe the invention in such terms as to enable one skilled in the art to make and use the invention. The test of enablement is whether one reasonably skilled in the art (1) could make and use the invention (2) from the disclosures in the patent coupled with information known in the art (3) without undue experimentation. In re Wands, 858 F.2d 731 (Fed. Cir. 1988); United States v. Telectronics, Inc., 857 F.2d 778 (Fed. Cir. 1988); M.P.E.P. § 2164.01. With regard to the second part of the test, one must bear in mind that "a patent need not teach, and preferably omits, what is well known in the art." Hybritech v. Monoclonal Antibodies, 802 F.2d 1367, 1384 (Fed.Cir.1986). Further, the Federal Circuit has explained that "[t]he key word is 'undue' and not 'experimentation'. . . . The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine." *In*

re Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Moreover, "[t]he fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation." MPEP 7th ed., rev. 2 § 2164.01 (citing *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983); see also *Massachusetts Institute of Technology vs. A.B. Fortia*, 774 F.2d 1104 (Fed. Cir. 1985) and *In re Wands*, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). Thus, the test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue *In re Angstadt*, 537 F.2d 498 (CCPA 1976).

The instant specification provides considerable guidance to enable a skilled artisan to make and use the claimed screening assays. Initially, the specification teaches that PAK polypeptides and the CHK pathway are involved in the biological processes relating to cell cycle regulation and cell growth (specification, pages 1-4). The specification also directly teaches that PAK polypeptides are p21 activated kinases involved in the regulation of cytoskeletal dynamics, i.e, cell proliferation (specification, page 2).

In addition, the specification describes in detail the characteristics of PAK polynucleotides and polypeptides and further provides representative examples of specific PAK polypeptides and polynucleotides that can be used in the cell culture assay systems, as well as providing their sequences. See specification at pages 4-7. In addition, the specification teaches one how to produce cells that express PAK polypeptides or nucleic acids at pages 8-10 and how to use them in cell proliferation and cell cycle assays at pages 24-25.

In addition, the specification describes agents that modulate the expression and/or activity of a PAK nucleic acid or polypeptide, including PAK-specific antibodies, PAK-specific antisense oligomers and other nucleic acid modulators, and chemical agents or small molecules that specifically bind to or interact with PAK, or compete with a PAK binding partner (specification, pages 12-19) and provides several specific examples of such agents (specification at pages 13-14 (small molecule modulating agents), pages 14-17 (protein modulating agents), and pages 18-19 (nucleic acid modulating agents).

Furthermore, the specification teaches that the assay system can be a cell-based assay and provides examples of cell-based assay systems, including cell proliferation

assay systems (specification at pages 24-25). In addition, the specification teaches one skilled in the art how to measure the expression and/or activity of PAK. For example, the specification teaches that a change in the expression of PAK can be determined using western blotting, immunoprecipitation, and immunohistochemical analyses to determine protein levels, as well as Taqman, RT-PCR, Northern blotting, and other analyses to determine mRNA levels (pages 36-39). The specification teaches that a change in the activity of PAK can be determined using kinase assays, such as the kinase assay described on pages 36-37, as well as other kinase assays well-known in the art.

In addition, with respect to claim 16, the specification provides numerous examples of assay systems that can be used to confirm that the test agent modulates the CHK pathway. (specification at pages 30-32).

Applicants submit that, based on the discussions presented above, there is ample support for the specification being enabling. Applicants assert that, using the guidance provided in the specification, one skilled in the art would be able to make and use the claimed screening assays. For the reasons set forth above, the claims are fully enabled and can be readily practiced by one skilled in the art. Accordingly, Applicant respectfully requests withdrawal of the 35 U.S.C. § 112, first paragraph, rejection.

CONCLUSION

In view of the above remarks, the application is considered to be in good and proper form for allowance and the Examiner is respectfully requested to pass this application to issue.

Respectfully submitted,
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